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Improvement of Clinical Staging in Cervical Cancer with Serum Squamous Cell Carcinoma Antigen and CA 125 Determinations

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Staging of cervical cancer is routinely performed by means of examination under anesthesia in combination with radiographic and/or endoscopic techniques. This "clinical" staging leads to 10–25% misclassification, mostly due to positive lymph nodes or lymph or blood vessel invasion. Determination of pretreatment squamous cell carcinoma antigen (SCC) and CA 125 serum levels may solve part of this staging problem and may improve the selection of the most appropriate individual therapy. Using 2.5 ng/ml (SCC) and 35 U/ml (CA 125) as cutoff levels, we studied 99 patients retrospectively. Elevated levels were found in 27% (SCC) and 23% (CA 125). In clinical stage IB or IIA disease 45/81 patients had positive nodes or lymph or blood vessel invasion at operation. Of these patients 49% had elevated serum levels of SCC or CA 125. Strongest correlation was found with blood vessel invasion (57%). Only 19% of low-stage patients without evidence of vascular spread of disease had positive levels. The positive predictive value of SCC and CA 125 for detection of vascular spread of disease in low-stage cervical cancer was 76%. In most centers surgery is the primary treatment of choice in low-stage cervical cancer. Nevertheless, with respect to patient survival, results of primary surgery and primary radiotherapy are comparable. Radiotherapy given in an adjuvant setting leads to a high incidence of severe complications. In order to overcome part of these complications one should consider radiotherapy as the primary therapy of choice in patients with clinical stage IB or IIA cervical cancer with elevated pretreatment SCC or CA 125 levels.

INTRODUCTION

Tumor staging is one of the most important aspects in the treatment of patients with oncological diseases. The type of treatment offered to a patient largely depends on the extension of the disease. Misclassification of stage may thus result in a suboptimal therapeutic approach. In most malignancies the stage of disease is defined following (extensive) surgery and histopathologic examination of all tissues removed. However, in the case of cervical cancer, staging of the disease is routinely performed by means of examination under anesthesia in combination with radiographic and/or endoscopic techniques. This type of staging is referred to as "clinical staging." The main reason for this clinical estimation of the extent of disease is the fact that in most centers radiotherapy is the primary treatment of choice for patients with locally advanced disease. In these cases a surgical intervention should be prevented since it may reduce the effectiveness of the additional radiation treatment and lead to a higher incidence of severe complications [1]. Examination under anesthesia is surely not a very accurate way to evaluate a patient's extent of disease. Especially, tumor spread beyond the small pelvis or lymph and blood vessel invasion cannot be detected with this type of staging. When clinical staging was compared with surgical staging, inaccuracies (mostly understaging) were found in 10–25% of patients with clinical stage IB or IIA [2–4]. Several authors have demonstrated reduced survival in patients with lymph node metastases and lymph or blood vessel invasion [5, 6]. It seems useful to develop new strategies to define subgroups of patients in order to further individualize treatment.

During the past decade a number of potentially useful serum tumor markers have been developed. Squamous cell carcinoma antigen (SCC) is a subfraction of the tumor antigen TA-4 and was isolated from a squamous cell carcinoma of the uterine cervix [7]. In prior studies of patients with squamous cell carcinoma of the cervix, SCC serum levels have been shown to correlate with stage of disease, to be predictive of response, and to aid in the detection of recurrence [8–10]. CA 125 is a tumor marker mainly used for the monitoring of treatment results in patients with ovarian cancer. However, the CA 125 antigenic determinant has also been reported to be present on adenocarcinoma of the endocervix. CA 125 serum levels were elevated in 50% of the patients with cervical adenocarcinoma [11].

The present study retrospectively analyzed the correlation between the serum levels of SCC and CA 125 and the post-surgery-determined extent of disease in patients with cervical cancer. Special attention was given to the predictability

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TABLE 1

Correlation between Stage of Cervical Cancer and Pretreatment Serum Levels of CA 125 and SCC

	N	SCC (ng/ml) median (range)	CA 125 (U/ml) median (range)
Stage I	63	1.6 (0.4–15)	15.0 (2.0–210)
Stage II	28	1.6 (0.5–34)	17.0 (3.8–910)
Stage III/IV	8	18.0 (0.6–70)	17.0 (9.7–1300)
All patients	99	1.7 (0.4–70)	15.0 (2.0–1300)

TABLE 2

SCC and CA 125 Pretreatment Serum Levels in Relation to Histopathological Diagnosis (Numbers above Indicated Cutoff)

	N	SCC > 2.5 (ng/ml)	CA 125 > 35 (U/ml)
Squamous cell carcinoma	67	19 (28%)	13 (19%)
Adenocarcinoma	20	4 (20%)	6 (30%)
Adenosquamous carcinoma	8	2 (25%)	2 (25%)
Others	4	1 (25%)	2 (50%)
All patients	99	26 (26%)	23 (23%)

of positive lymph nodes and/or vascular spread of disease in clinical stage IB and IIA cervical carcinoma. Thus, it was questioned whether determination of SCC and CA 125 serum levels can contribute to the selection of the most appropriate individual therapy.

MATERIALS AND METHODS

Medical records of 99 patients with histopathologically proven cervical cancer were studied. All patients attended the Department of Obstetrics and Gynecology of the University Hospital Nijmegen between 1983 and 1994. The ages of the 99 patients ranged from 20 to 81 years, median 41 years. Patients were clinically staged according to international FIGO (International Federation of Gynecology and Obstetrics) guidelines. Staging was routinely performed by means of examination under anesthesia in combination with radiographic and/or endoscopic techniques. The clinical stage of disease was FIGO stage IB in 63, IIA in 18, IIB in 10, III in 6, and IV in 2 patients. All the patients with stage IB or IIA and 3 patients with stage IIB were treated with radical surgery including retroperitoneal para-aortic and pelvic lymph node dissection. Overall, a median number of 24 lymph nodes were removed at operation. Patients that were not primarily operated received radiotherapy ($N = 15$). All patients with lymph node metastases, vascular invasion, and/or histopathologically positive resection margins received postoperative radiotherapy.

Pretreatment blood samples were drawn from each patient within 2 weeks before primary therapy and stored at −35°C until assayed. All the serum specimens were assayed for SCC and CA 125. The SCC antigen was measured using a microparticle enzyme immunoassay (IMx SCC; Abbott Laboratories, Diagnostic Division, Abbott Park, IL). A value of 2.5 ng/ml was chosen as the upper limit of normal. This cutoff level represents the 99th percentile in a group of 885 healthy subjects (data provided by manufacturer). CA 125 measurements were performed with the IMx CA 125 (Abbott Laboratories, Diagnostic Division). For this assay the internationally used cutoff level of 35 U/ml was chosen, being the 99th percentile in a normal population. Pretreatment serum values for SCC and CA 125 were compared with several clinical and histopathological parameters. Statistical analysis was performed using the Wilcoxon rank–sum test for comparison of the serum marker concentrations. The χ^2 test was used to investigate differences in the number of patients with elevated marker levels between subgroups.

RESULTS

Overall, elevated pretreatment levels of SCC and CA 125 were found in only 26 and 23% of all patients ($N = 99$), respectively. The combined use of both tumor markers resulted in positive values for one or both markers in 42% of the patients. Median pretreatment levels of CA 125 were in the same range for all clinical stages (15 U/ml), with a wide variation in each stage (Table 1). Median values for SCC were in the same range for stage I and II patients. However, significantly higher median values for SCC were found in advanced stage (III and IV) cervical cancer (Wilcoxon test: $P = 0.008$). In the subgroup of patients with squamous cell carcinoma ($N = 67$) elevated SCC levels were found in 28%, whereas CA 125 levels were elevated in only 19% of these patients (Table 2). In patients with adenocarcinoma ($N = 20$) CA 125 levels were elevated in 30% of the patients with SCC values being elevated in 20%. In only one patient tumor cell differentiation was reported to be grade 1. Elevated SCC levels were found in 26% of the cases with grade 2 and in 32% of the grade 3 cases (Table 3). This difference was not statistically significant (χ^2: $P = 0.52$). For CA 125 the difference was even smaller (20% for grade 2 and 27% for

TABLE 3

SCC and CA 125 Pretreatment Serum Levels in Relation to Differentiation (Numbers above Indicated Cutoff)

Differentiation	*N*	SCC > 2.5 ng/ml	CA 125 > 35 U/ml
1	1	1	0
2	54	14 (26%)	11 (20%)
3	34	11 (32%)	9 (27%)
Unknown	10	0	3 (30%)
All patients	99	26 (26%)	23 (23%)

TABLE 4

SCC and CA 125 Pretreatment Serum Levels in Relation to Tumor Size in 81 Patients with Stage IB and IIA Cervical Cancer (Median Value and Range)

	N	SCC (ng/ml)	CA 125 (U/ml)
<2 cm	23	1.6 (0.6–3.1)	13 (3.5–50)
>2 cm	54	1.5 (0.4–15)	17 (2.0–210)
Unknown	4	2.5 (0.9–7.3)	12 (5.6–27)

grade 3). The correlation between tumor size and pretreatment serum levels of both markers was studied in the group of patients with stage IB or IIA ($N = 81$). Median levels for tumors less than 2 cm in diameter were in the same range for both markers used, when compared with larger tumors (Table 4).

In the subgroup of patients with (clinical) stage IB and IIA ($N = 81$) 45 patients were found to have some histopathological evidence of vascular spread of tumor cells. Of these patients 13 (16%) were found to have positive lymph nodes. Thirty-three patients (41%) had invasion of lymph vessels, whereas 23 patients (28%) had signs of blood vessel invasion. Among the 13 patients with nodal disease only 1 patient had positive periaortic or common iliac nodes (1.2% of all stage IB and IIA patients). In this patient elevated serum levels were found for both markers. Overall, 22 of 45 patients (49%) with evidence of vascular (lymph or blood vessel) spread or nodal disease had pretreatment elevated serum levels of SCC or CA 125 (Table 5). Strongest correlation with elevated marker levels was found in the group with blood vessel invasion (57%). In the group with lymph vessel invasion 55% had positive levels of either SCC or CA 125, whereas in the group with positive lymph nodes 46% had positive levels. Of the stage IB and IIA patients with no evidence of vascular spread of tumor cells, only 19% (7/36) had positive serum levels. These data resulted in a positive predictive value of 76% (22/29) for the detection of some type of vascular spread in stage IB or IIA patients.

Progressive disease after primary treatment in patients with (clinical) stage IB or IIA was observed in 27% ($N = 22$) of the cases. Progression occurred between 1.4 and 104 months (median 10 months) after radical hysterectomy. Most of these patients (81.8%) had positive lymph nodes and/or lymph or blood vessel invasion at the time of radical surgery. Progressive disease was found in 56% of patients with elevated pretreatment CA 125 levels ($N = 16$), whereas only 19% of the patients with elevated SCC levels ($N = 16$) demonstrated progression.

DISCUSSION

The internationally accepted FIGO classification of cervical cancer, based on clinical staging, is an inaccurate way of defining a patient's extent of disease. This noninvasive approach leads to misclassification (mostly understaging) in a considerable number of cases (10–25%), possibly resulting in suboptimal care [2–4]. Patients with positive lymph nodes and/or clear lymph or blood vessel invasion comprise most of the misclassified cases. Most of these patients need adjuvant radiation treatment leading to a higher incidence of severe complications. Determination of pretreatment serum levels of tumor-associated antigens may help to improve the selection of the most appropriate therapy regimen for an individual patient. A panel of SCC and CA 125 was chosen to cover squamous as well as adenocarcinomatous type of cervical carcinoma. Following the recommendations of the manufacturer 2.5 ng/ml was chosen as a cutoff level for SCC leading to a specificity of 99%. When this value was used in other studies elevated serum levels were found in 44–57% of patients with cervical cancer [8, 9]. In our study the sensitivity of this marker for cervical cancer was only 26%, probably as a result of the relatively high number of low-stage patients (82% stage IB or IIA). In concordance with the results of Avall-Lundqvist *et al.* [9] serum CA 125 was elevated in only 23% of the patients. These results confirm that both SCC and CA 125 are not suitable for the primary detection (screening) of patients with cervical cancer.

Median serum levels of SCC were the same for stage I and stage II patients (Table 1). However, as found by others

TABLE 5

Correlation between SCC and CA 125 Serum Levels and Vascular Invasion in Patients ($N = 81$) with Stage IB and IIA (Numbers above Indicated Cutoff)

	N	SCC > 2.5 (ng/ml)	CA 125 > 35 (U/ml)	Either
Lymph nodes (+)	13	2 (15%)	5 (39%)	6 (46%)
Lymph nodes (−)	68	14 (21%)	11 (16%)	23 (34%)
Lymph vessel (+)	33	10 (30%)	11 (33%)	18 (55%)
Lymph vessel (−)	48	6 (13%)	5 (10%)	11 (23%)
Blood vessel (+)	23	7 (30%)	8 (35%)	13 (57%)
Blood vessel (−)	58	9 (16%)	8 (14%)	16 (28%)
Lymph node (+) and/or vascular invasion (+)	45	12 (27%)	13 (29%)	22 (49%)
Lymph node (−) and vascular invasion (−)	36	4 (11%)	3 (8.3%)	7 (19%)

[9, 12] significantly higher SCC levels were found for stage III and IV. The relatively small tumor bulk and the limited degree of infiltration may explain low marker levels in low-stage patients. In case of CA 125 the median levels were not stage dependent. In contrast with the results of Duk *et al.* [8], we did not find a correlation between tumor size and marker levels in a subpopulation of stage IB and IIA patients. Unlike SCC, the serum CA 125 level was found to be a useful indicator for progression. Of all 16 patients with stage IB and IIA disease who had pretreatment CA 125 levels >35 U/ml, 9 patients (56%) demonstrated progression during follow-up.

Of the group of stage IB and IIA ($N = 81$), 45 patients were found to have lymph node metastases or lymph or blood vessel invasion. These data are in line with other studies. Overall, 49% of these patients had elevated pretreatment SCC or CA 125 levels. On the other hand only 19% of patients without evidence of vascular spread had elevated serum levels. Thus, a panel of SCC and CA 125 seems to be a useful marker in predicting the presence of vascular spread of disease. However, in 1 of 5 patients without tumor spread a false positive prediction will be made. Of all stage IB and IIA patients with positive pretreatment values ($N = 29$) 22 patients were found to have vascular tumor spread resulting in a positive predictive value of 76%. At present results of primary surgery on the one hand and radiotherapy on the other as the primary treatment modality in low-stage cervical cancer are comparable. Since postoperative radiotherapy leads to a higher incidence of severe complications one should consider radiation treatment as the primary treatment of choice in stage IB and IIA cervical cancer patients with elevated SCC and or CA 125 serum levels.

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